International Journal of Chronic Obstructive Pulmonary Disease Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Comparison of Infection Risks Between Various Inhaled and Intranasal Corticosteroids: A Pharmacovigilance Analysis Based on the FAERS Database

Ying Lan[1], Die Hu[1], Shijing Huang[1], Qing Ma[1], Li Chen[2,3], Min Xu[1], Qin He[1]

[1]Department of Pharmacy, Affiliated Hospital of Southwest Jiaotong University, The Third People's Hospital of Chengdu, Chengdu, Sichuan, 610031, People's Republic of China; [2]Department of Pharmacology, Faculty of Medicine, University of the Basque Country, UPV/EHU, Leioa, Spain; [3]Department of Pharmacy and Evidence-Based Pharmacy Center, West China Second University Hospital, Sichuan University, Chengdu, People's Republic of China

Correspondence: Ying Lan; Li Chen, Email lanying0212@126.com; chenl_hxey@scu.edu.cn

Purpose: This study conducted a pharmacovigilance analysis based on the FDA Adverse Event Reporting System (FAERS) database to compare the infection risk of inhaled or nasal Beclomethasone, Fluticasone, Budesonide, Ciclesonide, Mometasone, and Triamcinolone Acetonide.

Methods: We used proportional imbalance analysis to evaluate the correlation between ICS /INCs and infection events. The data was extracted from the FAERS database from April 2015 to September 2023. Further analysis was conducted on the clinical characteristics, site of infection, and pathogenic bacteria of ICS and INCs infection adverse events (AEs). We used bubble charts to display their top 5 infection adverse events.

Results: We analyzed 21,837 reports of infection AEs related to ICS and INCs, with an average age of 62.12 years. Among them, 61.14% of infection reports were related to females. One-third of infections reported to occur in the lower respiratory tract with Fluticasone, Budesonide, Ciclesonidec, and Mometasone; over 40% of infections reported by Triamcinolone Acetonide were eye infections; the rate of oral infections caused by Beclomethasone were 7.39%. The reported rates of fungal and viral infections caused by beclomethasone were 21.15% and 19.2%, respectively. The mycobacterial infections caused by Budesonide and Ciclesonidec account for 3.29% and 2.03%, respectively. Bubble plots showed that the ICS group had more fungal infections, oral infections, pneumonia, tracheitis, etc. The INCs group had more eye symptoms, rhinitis, sinusitis, nasopharyngitis, etc.

Conclusion: Women who use ICS and INCs are more prone to infection events. Compared to Budesonide, Fluticasone seemed to have a higher risk of pneumonia and oral candidiasis. Mometasone might lead to more upper respiratory tract infections. The risk of oral infection was higher with Beclomethasone. Beclomethasone causes more fungal and viral infections, while Ciclesonide and Budesonide are more susceptible to mycobacterial infections.

Keywords: data mining, FAERS, ICS, INCs, pharmacovigilance, infections

Introduction

Inhaled corticosteroids (ICS) can reduce airway inflammation and are commonly used medicine for chronic airway diseases such as chronic obstructive pulmonary disease (COPD) and asthma.[1,2] Intranasal corticosteroids (INCs) are the first-line treatment for allergic rhinitis (AR).[3] ICS and INCs usually require long-term use, and some patients may even require lifelong medication. However, the long-term use of corticosteroids may bring about the risk of adverse drug events. Among them, respiratory tract infections, infections caused by fungus, mycobacteria, and other pathogens have attracted high attention and concern from clinical and public.[4,5] Currently, commonly used ICS or INCs include Budesonide, Triamcinolone Acetonide, Beclomethasone Propionate, Mometasone Furoate, Fluticasone Propionate or

Received: 29 February 2024
Accepted: 18 June 2024
Published: 25 June 2024

Furoate, and Ciclesonide. However, there was no conclusive evidence to compare the risk of infection among various ICS and INCs at different levels of pathogens, infection sites, and dosage forms.

Food and Drug Administration Adverse Event Reporting System (FAERS) database is a public, accessible, and free database in the United States, containing tens of thousands of voluntary adverse event reports submitted by health professionals, consumers, manufacturers, and others, aimed at supporting the Food and Drug Administration (FDA)'s safety monitoring of post-market drugs and biological products.[6,7] The signal mining of FEARS data is a recognized and widely used research method for pharmacovigilance analysis.[8] To further explore the incidence of infection among ICS and INCs users in the real world, we mined adverse event (AE) risk signals from the FAERS database.

Materials and Methods

Data Sources

This study analyzes the adverse reactions and medication errors reported voluntarily in the FDA Advance Event Reporting System (FAERS) database. The FAERS database is updated quarterly and includes 7 data files: patient demographic and administrative information (DEMO), drug information (DRUG), coded for the adverse events (REAC), patient outcomes (OUTC), report sources (RPSR), therapy start dates and end dates for reported drugs (THER), and indications for drug administration (INDI), and deleted cases. The classification and standardization of Adverse events (AEs) in the FAERS data are based on the Medical Dictionary for Regulatory Activities 26.1 (MedDRA).[9] Each report is coded using preferred terms (PTs), which can be assigned to one or more High-level Terms (HLT), High-level Group Terms (HLGT), and System Organ Class levels (SOC) within MedDRA.

Data Processing and AE Signal Detection

In our study, the reports submitted from Apr. 2015 to Sep. 2023 in the FAERS database were extracted, with the drug records of "Beclomethasone", "Fluticasone", "Budesonide", "Mometasone", "Ciclesonide", "Triamcinolone" and their compound drugs. Two researchers processed the data, including deduplication, categorizing related AEs by standardized MedDRA query and PT, and extracting Clinical characteristic information (gender, age, reporting area, reporter, administration pathway, dosage form, etc.) from the reports.

Statistical Analysis

Disproportionality analysis is widely used in pharmacovigilance studies to identify potential signals, conducted by computing the number of reports(N), the proportional reporting ratio (PRR), the reporting odds ratio (ROR), and χ^2 (chi-square). The larger the N, PRR, ROR, or χ^2, the stronger the correlation signal. According to the criteria established by Evans et al, a positive signal of disproportionality was defined as a PRR $\geq$2, a $\chi^2 \geq 4$, a 95% confidence interval of the reporting odds ratio (ROR) >1, and at least 3 cases.[10] This study sorted the mined AE signals according to N, ROR, and χ^2, and displayed the results as a bubble chart. The abscissa was $\log_2$ROR, and the ordinate was the square root of the χ^2 value. All points in the figure represented the adverse reaction signals mined, and the size of the points represented the number of reported cases of the adverse reaction.

Results

Descriptive Analysis

After deduplication and dosage form screening, 151,515 total cases (487,724 reports) and 21,837 infections (25,918 reports) associated with inhaled corticosteroids and intranasal corticosteroids were obtained. The characteristics of these 21,837 cases are summarized in Table 1. The chart showed little difference in patient characteristics between each corticosteroid. Most cases came from North America (81.12%), mainly reported by Consumers (69.06%). Females (61.14%) were more numerous than males (29.32%), but 9.54% of gender data was missing. In addition, except for 41.47% of age data not available, the average age was 62.12 years old.

Table 1 Clinical Characteristics of Reports with Inhaled Corticosteroids and Intranasal Corticosteroids-Associated Infections from the FAERS Database (Apr. 2015 to Sep. 2023)

Characteristics	Total (N, %)	Beclomethasone (N, %)	Fluticasone (N, %)	Budesonide (N, %)	Ciclesonide (N, %)	Mometasone (N, %)	Triamcinolone (N, %)
Number of infected patients	21,837	395	11,355	8381	503	821	382
Sex of patient							
Female	13,413 (61.14%)	281 (71.14%)	6825 (60.11%)	5274 (62.93%)	309 (61.43%)	524 (63.82%)	200 (44.46%)
Male	6402 (29.32%)	105 (26.58%)	3140 (27.65%)	2606 (31.09%)	190 (37.77%)	255 (31.06%)	106 (28.37%)
Unknown	2022 (9.54%)	9 (2.28%)	1390 (12.24%)	501 (5.98%)	4 (0.8%)	42 (5.12%)	76 (27.16%)
Age group (years)							
<18	503 (2.32%)	30 (7.59%)	167 (1.47%)	247 (2.94%)	6 (1.19%)	37 (4.51%)	16 (4.33%)
19~65	5877 (26.88%)	77 (19.49%)	2181 (19.21%)	2965 (35.38%)	240 (47.71%)	298 (36.3%)	116 (28.03%)
>65	6422 (29.33%)	80 (20.25%)	2961 (26.08%)	2924 (34.89%)	178 (35.39%)	195 (23.75%)	84 (21.45%)
Unknown	9035 (41.47%)	208 (52.66%)	6046 (53.25%)	2245 (26.79%)	79 (15.71%)	291 (35.44%)	166 (46.19%)
Mean age	62.12	53.31	64.51	61.15	59.69	56.75	56.62
Reporting region							
Europe	1499 (6.97%)	40 (10.13%)	520 (4.58%)	804 (9.6%)	47 (9.34%)	69 (8.4%)	19 (9.52%)
North America	17,774 (81.12%)	343 (86.83%)	9359 (82.42%)	6639 (79.21%)	418 (83.1%)	671 (81.73%)	344 (76.99%)
Asia	1308 (6.14%)	4 (1.01%)	813 (7.16%)	411 (4.9%)	20 (3.98%)	47 (5.72%)	13 (10.03%)
South America	840 (3.82%)	6 (1.52%)	460 (4.05%)	351 (4.19%)	0 (0%)	21 (2.56%)	2 (0.52%)
Africa	42 (0.21%)	0 (0%)	19 (0.17%)	21 (0.25%)	0 (0%)	1 (0.12%)	1 (0.87%)
Oceania	151 (0.72%)	0 (0%)	113 (1%)	29 (0.35%)	5 (1%)	3 (0.37%)	1 (1.38%)
Unknown	223 (1.02%)	2 (0.51%)	71 (0.62%)	126 (1.5%)	13 (2.58%)	9 (1.1%)	2 (0.69%)
Reporters							
Consumer	15,190 (69.06%)	341 (86.33%)	9802 (86.32%)	4208 (50.21%)	250 (49.7%)	373 (45.44%)	216 (42.04%)
Health professional	1115 (5.33%)	6 (1.52%)	183 (1.61%)	692 (8.26%)	101 (20.08%)	83 (10.11%)	50 (18.86%)
Lawyers	8 (0.05%)	0 (0%)	4 (0.04%)	1 (0.01%)	0 (0%)	2 (0.24%)	1 (0.87%)
Physician	3135 (14.63%)	17 (4.3%)	966 (8.51%)	1694 (20.21%)	134 (26.64%)	235 (28.62%)	89 (30.62%)
Pharmacists	308 (1.41%)	13 (3.29%)	150 (1.32%)	84 (1%)	5 (0.99%)	54 (6.58%)	2 (0.69%)
Others	633 (2.93%)	15 (3.8%)	201 (1.77%)	326 (3.89%)	3 (0.6%)	69 (8.4%)	19 (5.36%)
Unknown	1448 (6.59%)	3 (0.76%)	49 (0.43%)	1376 (16.42%)	10 (1.99%)	5 (0.61%)	5 (1.56%)

Abbreviation: N, number of reports.

Comparative Analysis

There were 487, 14,642, 8381, 991, 1183, and 48,110 infection reports related to Beclomethasone, Fluticasone, Budesonide, Mometasone, Ciclesonide, Triamcinolone, respectively. The proportion of infection reports of Ciclesonide was 7.98%, which was significantly higher than that of Mometasone (2.69%) and Triamcinolone Acetonide (3.89%) (Table 2). The reports of Budesonide and Fluticasone mainly came from inhalation preparations, and the top five infection reports of the two drugs were primarily related to airway and fungal infections. The top five infections reported with nasal Triamcinolone Acetonide were mainly eye and nasal infections.

Table 2 The Proportion of Infection Reports and the Top 5 Infection Reports

	All Reports (N)	Infection Reports (N)	Constituent Ratio	Top 5 Infection Reports [N, χ^2, ROR (95% CI)]
Beclomethasone	9738	487	5.00%	Candida infection 48, 44.14, (12.16,21.53) Sinusitis 39, 33.39, (1.79,3.37) Bronchitis 34, 44.13, (2.12,4.17) Oral candidiasis 25, 304.99, (9.62,21.17) Fungal infection 13, 11.0, (1.42,4.21)
Fluticasone	258,702	14,642	5.66%	Pneumonia 3212, 2131.83, (2.18,2.34) Bronchitis 991,1252.95, (2.79,3.17) Candida infection 966, 8662.42, (11.07,12.64) Oral candidiasis 569, 5127.21, (10.87,12.91) Lung infection 252, 396.11, (2.93,3.76)
Budesonide	150,475	8381	5.57%	Pneumonia 1296, 1551.39, (2.76,3.08) Bronchitis 690, 3198.99, (6.18,7.2) Nasopharyngitis 573, 328.89, (1.95,2.3) Sinusitis 441, 580.97, (2.74,3.31) Candida infection 378, 4380.18, (12.69,15.6)
Ciclesonide	12,424	991	7.98%	Pneumonia 144, 758.86, (6.54,9.23) Sinusitis 80, 820.01, (10.23,16.08) Nasopharyngitis 62, 205.05, (4.09,6.81) Lower respiratory tract infection 57, 1009.65, (15.7,26.7) Infection 54, 219.11, (4.62,7.96)
Mometasone	44,019	1183	2.69%	Candida infection 37, 60.41, (2.42,4.62) Oral candidiasis 30, 84.73, (3.23,6.63) Rhinitis 20, 54.21, (2.9,6.99) Laryngitis 16, 18.61, (1.72,4.6) Chronic sinusitis 13, 63.35, (3.92,11.67)
Triamcinolone	12,366	481	3.89%	Nasopharyngitis 37, 4.81, (0.96,0.96) Sinusitis 27, 0.09, (1.38,1.38) Septic shock 25, 17.49, (3.35,3.35) Eye pruritus 23, 22.37, (3.9,3.9) Ocular hyperaemia 21, 5.65, (1.09,2.57)

Abbreviation: N, number of reports.

Stratified Analysis Based on Different Infection Sites

Beclomethasone, Budesonide, Fluticasone, Ciclesonide, and Mometasone which were mainly inhaled preparations, had over 50% respiratory infections reports. Lower respiratory tract infections such as pneumonia or bronchitis were significant adverse events that cannot be ignored. Nearly one-third of all infection reports for Fluticasone, Budesonide, Ciclesonide, and Mometasone were lower respiratory tract infections. Triamcinolone Acetonide (nasal or dose form unknown) might be associated with infections in the eyes, pharynx, and nose, with reports of eye infections accounting for over 40% (Table 3).

Stratified Analysis Based on Different Pathogens

About two-thirds of the infection reports for each drug had not identified the pathogen (Table 4). In reports of identified pathogens, the reported proportion of fungal infections caused by Beclomethasone (21.15%) was higher than other corticosteroids, while Ciclesonide (5.25%) and Triamcinolone Acetonide (7.28%) were relatively lower. In terms of the

Table 3 Analysis of Infection Reports from Infection Sites

Infection Site	Total (N, %)	Beclomethasone (N, %)	Fluticasone (N, %)	Budesonide (N, %)	Ciclesonide (N, %)	Mometasone (N, %)	Triamcinolone (N, %)
Oral cavity	1121	36 (7.39%)	786 (5.37%)	235 (2.8%)	14 (1.41%)	41 (3.47%)	9 (1.87%)
Eye	1501	48 (9.86%)	755 (5.16%)	336 (4.01%)	75 (7.57%)	87 (7.35%)	200 (41.58%)
Ear	176	8 (1.64%)	102 (0.7%)	52 (0.62%)	4 (0.4%)	8 (0.68%)	2 (0.42%)
Respiratory system	16,392	254 (52.16%)	9360 (63.93%)	5230 (62.4%)	627 (63.27%)	802 (67.79%)	119 (24.74%)
Pharynx	2322	35 (7.19%)	1356 (9.26%)	668 (7.97%)	69 (6.96%)	149 (12.6%)	45 (9.36%)
Larynx	377	7 (1.44%)	240 (1.64%)	110 (1.31%)	2 (0.2%)	16 (1.35%)	2 (0.42%)
Nasal Cavity	1874	46 (9.45%)	850 (5.81%)	655 (7.82%)	150 (15.14%)	132 (11.16%)	41 (8.52%)
Lower respiratory tract	8532	84 (17.25%)	5155 (35.21%)	2648 (31.6%)	279 (28.15%)	351 (29.67%)	15 (3.12%)
Respiratory infections with unclear location	3287	82 (16.84%)	1759 (12.01%)	1149 (13.71%)	127 (12.82%)	154 (13.02%)	16 (3.33%)
Circulatory system	436	4 (0.82%)	225 (1.54%)	151 (1.8%)	10 (1.01%)	12 (1.01%)	34 (7.07%)
Skin and soft tissue	391	11 (2.26%)	170 (1.16%)	163 (1.94%)	2 (0.2%)	24 (2.03%)	21 (4.37%)
Bones and joints	61	0 (0%)	30 (0.2%)	22 (0.26%)	2 (0.2%)	1 (0.08%)	6 (1.25%)
Digestive system	713	16 (3.29%)	418 (2.85%)	219 (2.61%)	25 (2.52%)	26 (2.2%)	9 (1.87%)
Urinary system	547	6 (1.23%)	346 (2.36%)	180 (2.15%)	7 (0.71%)	8 (0.68%)	0 (0%)
Reproductive system	82	1 (0.21%)	46 (0.31%)	25 (0.3%)	1 (0.1%)	5 (0.42%)	4 (0.83%)
Central nervous system	60	1 (0.21%)	17 (0.12%)	38 (0.45%)	1 (0.1%)	1 (0.08%)	2 (0.42%)
Unclear site of infection	4438	102 (20.94%)	2301 (15.72%)	1613 (19.25%)	192 (19.37%)	155 (13.1%)	75 (15.59%)

Note: %, the proportion of infection reports to the total reports of this drug.
Abbreviation: N, number of reports.

Table 4 Analysis of Infection Reports from Different Pathogens

Pathogen	Total	Beclomethasone (N, %)	Fluticasone (N, %)	Budesonide (N, %)	Ciclesonide (N, %)	Mometasone (N, %)	Triamcinolone (N, %)
Fungi	3710	103 (21.15%)	2361 (16.12%)	1038 (12.39%)	52 (5.25%)	121 (10.23%)	35 (7.28%)
Virus	3516	94 (19.3%)	1800 (12.29%)	1307 (15.59%)	124 (12.51%)	157 (13.27%)	34 (7.07%)
Bacterium	1139	18 (3.7%)	585 (4%)	448 (5.35%)	26 (2.62%)	38 (3.21%)	24 (4.99%)
Mycobacterium	414	2 (0.41%)	81 (0.55%)	276 (3.29%)	30 (3.03%)	22 (1.86%)	3 (0.62%)
Parasite	22	0 (0%)	7 (0.05%)	1 (0.01%)	3 (0.3%)	0 (0%)	11 (2.29%)
Pathogen unknown	17,117	270 (55.44%)	9722 (66.4%)	5194 (61.97%)	725 (73.16%)	832 (70.33%)	374 (77.75%)

Note: %, the proportion of infection reports to the total reports of this drug.
Abbreviation: N, number of reports.

proportion of reported viral infections, Beclomethasone (19.3%) was slightly higher than Fluticasone (12.29%), Budesonide (15.59%), Ciclesonide (12.51%), and Mometasone (13.27%), while triamcinolone acetonide (7.07%) was the lowest. The reported proportion of mycobacterium infection in Budesonide (3.29%) and Ciclesonide (3.03%) was higher than in other corticosteroids.

Stratified Analysis Based on Different Dose Forms

As shown in Table 5, the proportion of infection reports for inhalations of Budesonide monotherapy (10.92%) and Fluticasone monotherapy (9.52%) was higher than that of other compound inhaled formulations (<7%). Except for the nasal preparation of Ciclesonide (6.55%) and Mometasone (5.5%), the proportion of infection reports of other INCs was relatively low. Glycopyrrolate/Indacaterol/Mometasone were three combination inhalation formulations, with a significantly higher proportion of infection reports than the other two or three drug compound inhalation formulations. Figures 1 to 6 show the adverse reaction signal mining results of inhaled and nasal Beclomethasone, Fluticasone, Budesonide, Ciclesonide, Mometasone, and Triamcinolone respectively.

The signal strength for inhalation and nasal use of Beclomethasone are shown in Figure 1. The top five signals with higher intensity for inhaled Beclomethasone included Candida infection (N=48, ROR=190.05, χ^2=7660.13), Oral candidiasis (N=23, ROR=142.36, χ^2=2989.39), Oral fungal infection(N=6, ROR=159.83, χ^2=925.64), Bronchitis (N=32, ROR=31.24, χ^2=843.72) and Oral infection (N=4, ROR=79.65, χ^2=306.18), while for nasal use including eye pruritus (N=4, ROR=492.472, χ^2=1817.93), Conjunctival hyperemia (N=21, ROR=123.40, χ^2=1592.90), Ocular hyperemia (N=3, ROR=128.57, χ^2=359.20), Coronavirus infection (N=6, ROR=79.57, χ^2=415.48) and Sinusitis(N=6, ROR=56.26, χ^2=290.73).

The signal strength for inhalation and nasal use of Fluticasone are shown in Figure 2. The top five signals with higher intensity for inhaled Fluticasone included Candida infection (N=938, ROR=119.54, χ^2=91,761.85), Oral candidiasis (N=542, ROR=112.88, χ^2=52,204.79), Pneumonia (N=3166, ROR=29.73, χ^2=59,809.87), Bronchitis (N=952,

Table 5 Analysis of Infection Reports from Dose Forms

Drug	Component	Dose Form (N, %)		
		Inhalation	Nasal	Unknown
Beclomethasone	Beclomethasone	482 (6.26%)	5 (0.32%)	/
Fluticasone	Fluticasone (propionate or furoate)	2714 (9.52%)	21 (0.05%)	5 (0.47%)
	Fluticasone (furoate or propionate) \ Salmeterol	6759 (6.81%)	/	/
	Fluticasone \ Vilanterol	2683 (5.53%)	/	/
	Fluticasone \ Formoterol	0 (0%)	/	/
	Fluticasone \ Umeclidinium \ Vilanterol	2460 (6.36%)	/	/
Budesonide	Budesonide	2737 (10.92%)	32 (1.22%)	7 (0.05%)
	Budesonide \ Formoterol	5120 (5.34%)	/	/
	Budesonide \ Indacaterol	3 (11.11%)	/	/
	Budesonide \ Formoterol \ Glycopyrronium	482 (3.56%)	/	/
Ciclesonide	Ciclesonide	709 (7.89%)	184 (6.55%)	98 (15.63%)
Mometasone	Mometasone	205 (1.11%)	321 (5.5%)	109 (9.73%)
	Formoterol \ Mometasone	496 (2.79%)	/	/
	Mometasone \ Olopatadine	/	2 (0.56%)	/
	Indacaterol \ Mometasone	0 (0%)	/	/
	Glycopyrronium \ Indacaterol \ Mometasone	50 (12.76%)	/	/
Triamcinolone	Triamcinolone	/	207 (2.56%)	274 (6.42%)

Note: %, the proportion of infection reports to the total reports of this drug formulation.
Abbreviation: N, number of reports.

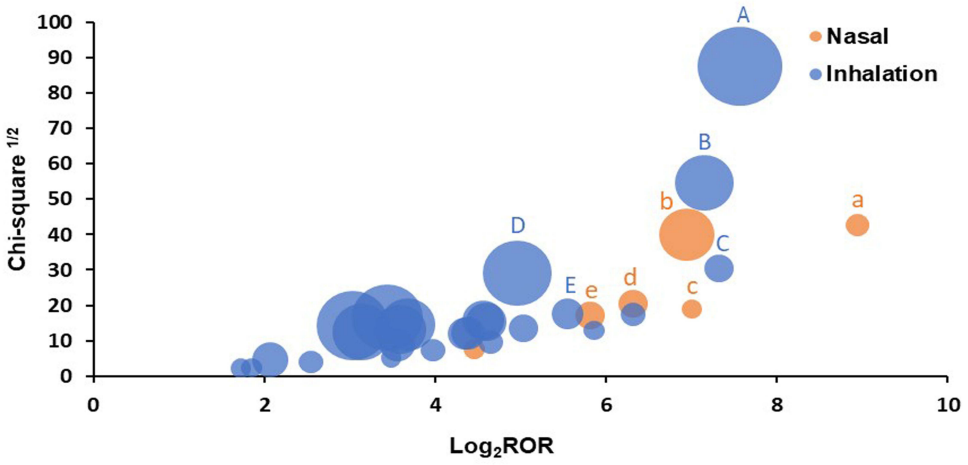

Figure 1 Signal strength for inhalation and nasal use of beclomethasone in FAERS.
Notes: A: Candida infection, B: Oral candidiasis, C: Oral fungal infection, D: Bronchitis, E: Oral infection, a: Eye pruritus, b: Conjunctival hyperemia, c: Ocular hyperemia, d: Coronavirus infection, e: Sinusitis.

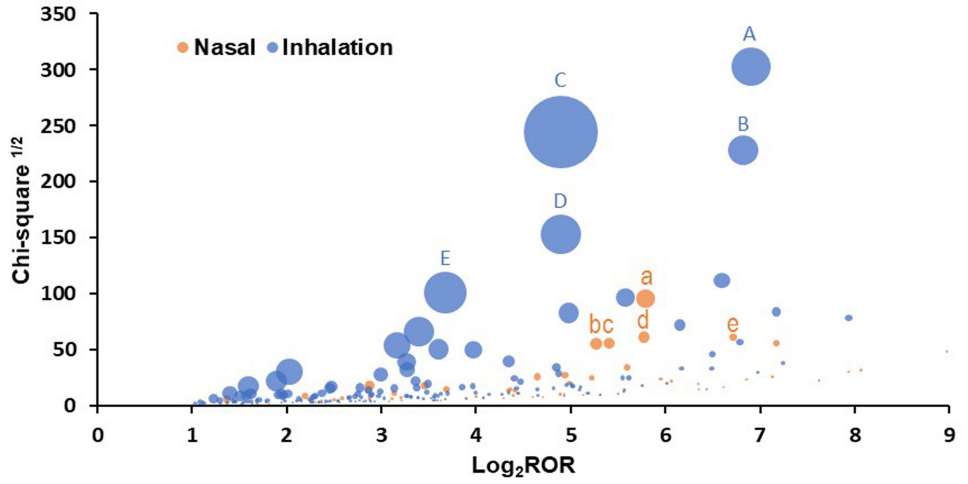

Figure 2 Signal strength for inhalation and nasal use of fluticasone in FAERS.
Notes: A: Candida infection, B: Oral candidiasis, C: Pneumonia, D: Bronchitis, E: Nasopharyngitis, a: Sinusitis, b: Eye irritation, c: Ocular hyperaemia, d: Eye pruritus, e: Rhinitis.

ROR=29.79, χ^2=23,495.85) and Nasopharyngitis(N=1056, ROR=12.78, χ^2=10,193.83), while for nasal use including Sinusitis (N=218, ROR=55.47, χ^2=9155.46), Eye irritation (N=93, ROR=38.61, χ^2=3090.34313117874), Ocular hyperemia (N=85, ROR=42.34, χ^2=3137.51), Eye pruritus (N=78, ROR=54.60, χ^2=3776.63), and Rhinitis (N=38, ROR=105.27, χ^2=3747.41)(Figure 2).

The signal strength for inhalation and nasal use of Budesonide are shown in Figure 3. The top five signals with higher intensity for inhaled Budesonide included Candida infection (N=365, ROR=84.92, χ^2=27,228.65), Bronchitis (N=650, ROR=41.30, χ^2=22,035.02), Pneumonia (N=1205, ROR=19.88, χ^2=16,508.20), Tuberculosis (N=204, ROR=70.02, χ^2=12,962.60) and Nasopharyngitis (N=558, ROR=13.33, χ^2=5655.80), while for nasal use including Sinusitis (N=26, ROR=61.47, χ^2=1190.22), Herpes simplex oesophagitis (N=3, ROR=2716.76, χ^2=7737.79), Laryngitis (N=9, ROR=184.49, χ^2=1509.25), Pharyngitis (N=7, ROR=115.00, χ^2=741.29) and Bronchitis (N=9, ROR=24.74, χ^2=188.63) (Figure 3).

The signal strength for inhalation and nasal use of Ciclesonide are shown in Figure 4. The top five signals with higher intensity for inhaled Ciclesonide included Pneumonia (N=90, ROR=21.30, χ^2=1314.79), Sinusitis (N=55, ROR=36.16,

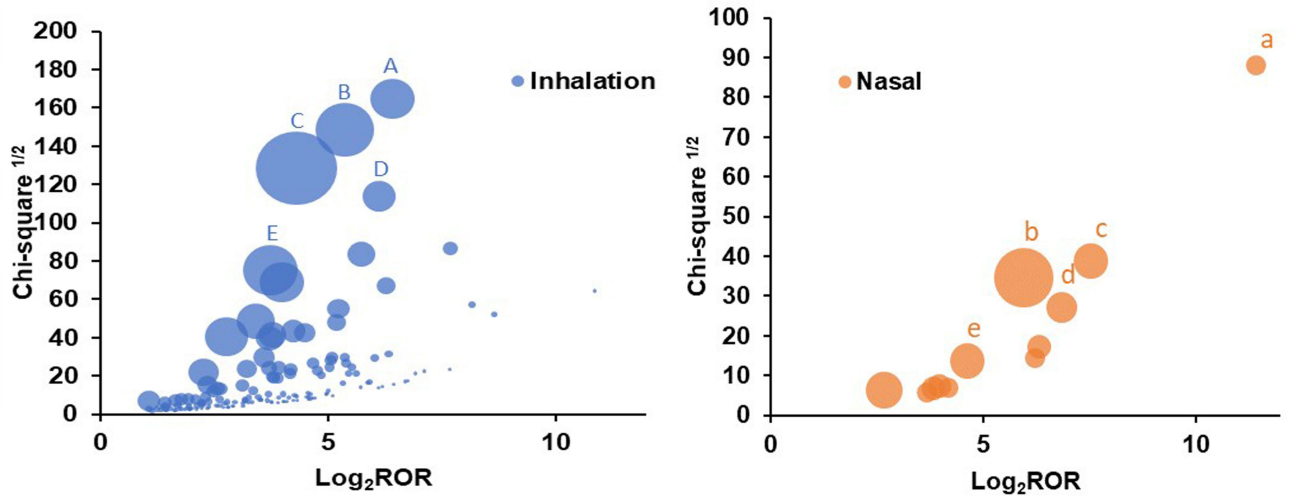

Figure 3 Signal strength for inhalation and nasal use of budesonide in FAERS.
Notes: A: Candida infection, B: Bronchitis, C: Pneumonia, D: Tuberculosis, E: Nasopharyngitis, a: Sinusitis, b: Herpes simplex oesophagitis, c: Laryngitis, d: Pharyngitis, e: Bronchitis.

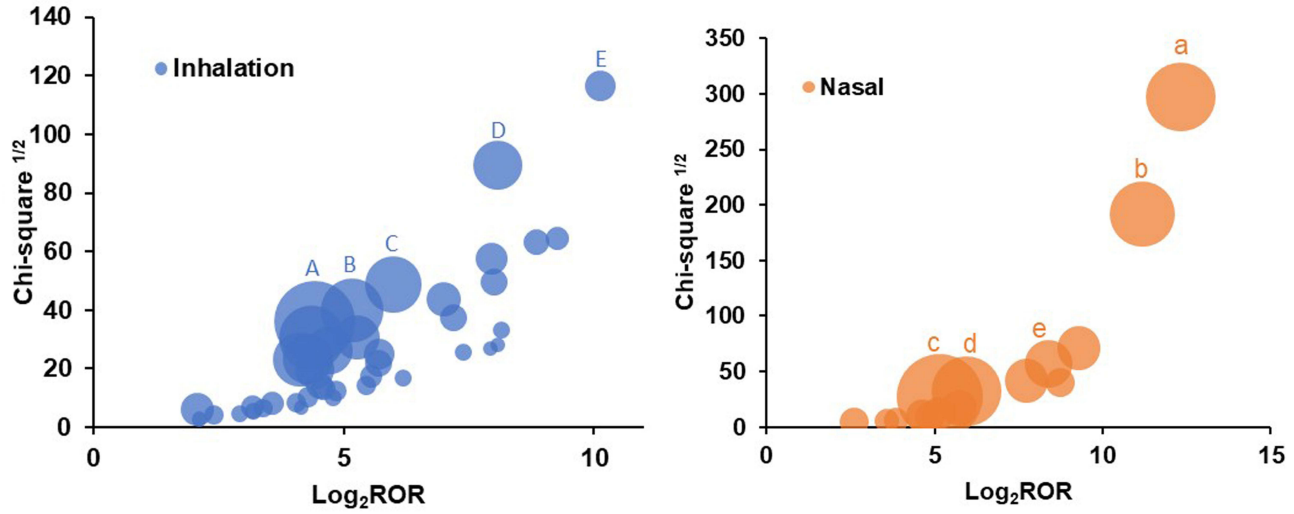

Figure 4 Signal strength for inhalation and nasal use of ciclesonide in FAERS.
Notes: A: Pneumonia, B: Sinusitis, C: Lower respiratory tract infection, D: Rhinitis, E: Bacterial disease carrier, a: Sinusitis, b: Mycobacterium avium complex infection, c: Pneumonia, d: Conjunctivitis allergic, e: Rhinitis.

χ^2=1597.77), Lower respiratory tract infection (N=44, ROR=63.74, χ^2=2388.25), Rhinitis (N=33, ROR=270.14, χ^2=7995.63) and Bacterial disease carrier (N=13, ROR=1123.79, χ^2=13,620.92), while for nasal use including Sinusitis (N=23, ROR=61.43, χ^2=1052.46), Mycobacterium avium complex infection (N=20, ROR=2329.72, χ^2=36,680.95), Pneumonia (N=35, ROR=35.42, χ^2=760.76), Conjunctivitis allergic (N=23, ROR=5156.16, χ^2=88,392.57) and Rhinitis (N=11, ROR=337.27, χ^2=3274.22) (Figure 4).

The signal strength for inhalation and nasal use of Mometasone are shown in Figure 5. The top five signals with higher intensity for inhaled Mometasone included Pneumonia (N=151, ROR=25.42, χ^2=2553.14), Nasopharyngitis (N=93, ROR=22.96, χ^2=1617.00), Bronchitis (N=60, ROR=35.63, χ^2=1793.13), Candida infection (N=36, ROR=77.94, χ^2=2544.49) and Oral candidiasis (N=28, ROR=101.90, χ^2=2641.66), while for nasal use including Sinusitis (N=30, ROR=30.25, χ^2=739.311), Nasopharyngitis (N=27, ROR=14.45, χ^2=298.99), Lower respiratory tract

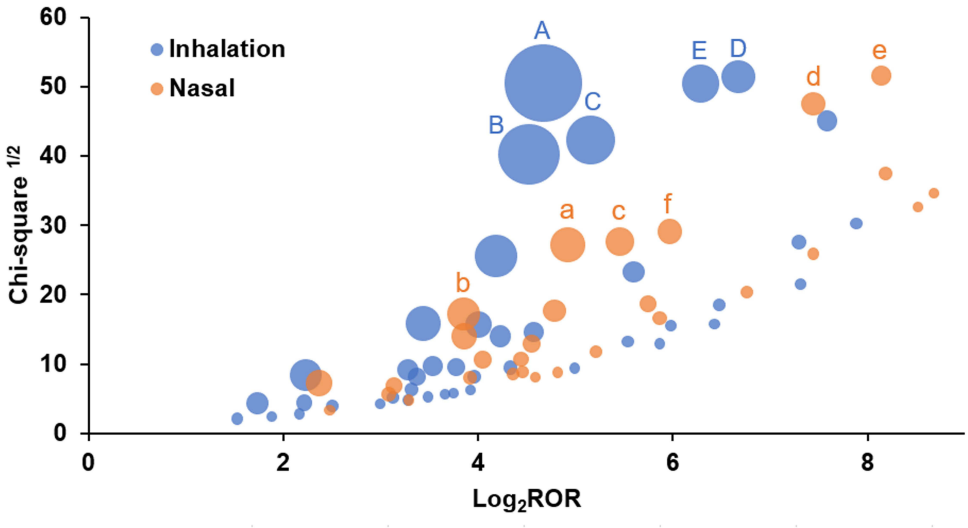

Figure 5 Signal strength for inhalation and nasal use of mometasone in FAERS.
Notes: A: Pneumonia, B: Nasopharyngitis, C: Bronchitis, D: Candida infection, E: Oral candidiasis, a: Sinusitis, b: Nasopharyngitis, c: Lower respiratory tract infection, d: Rhinitis, e: Chronic sinusitis, f: Pneumonia aspiration.

infection (N=20, ROR=43.82, χ^2=764.812), Rhinitis (N=14, ROR=173.77, χ^2=2253.85), Chronic sinusitis (N=10, ROR=281.65, χ^2=2663.20) and Pneumonia aspiration (N=15, ROR=62.47, χ^2=848.18) (Figure 5).

The signal strength for inhalation and nasal use of Triamcinolone are shown in Figure 6. The top five signals with higher intensity included Nasopharyngitis (N=35, ROR=59.67, χ^2=1311.85), Sinusitis (N=22, ROR=58.01, χ^2=961.05), Eye pruritus (N=21, ROR=176.40, χ^2=2890.13), Ocular hyperaemia (N=20, ROR=117.28, χ^2=1843.20), eye irritation (N=17, ROR=79.41, χ^2=1091.86) and Rhinitis (N=8, ROR=237.13, χ^2=1727.47) (Figure 6).

Discussions

Long-term use of corticosteroids could lead to infection, which is a well-known adverse drug reaction and a concern for physicians and patients. Currently, multiple clinical trials or systematic reviews based on clinical trials have shown that ICS can cause adverse reactions such as pneumonia, oral candidiasis, and mycobacterial infections. However, due to the

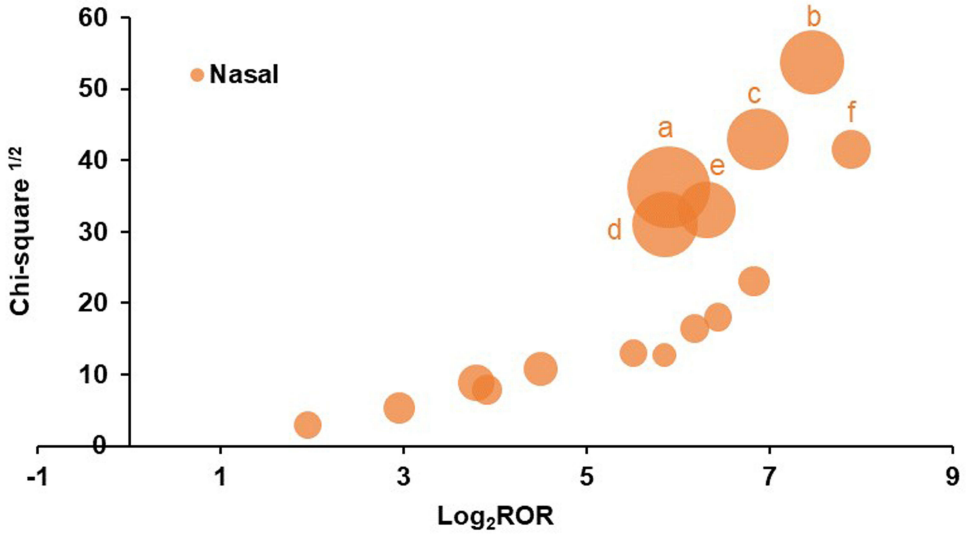

Figure 6 Signal strength for nasal use of triamcinolone in FAERS.
Notes: a: Nasopharyngitis, b:Sinusitis, c: Eye pruritus, d: Ocular hyperemia, e: Eye irritation, f: Rhinitis.

limitations of clinical trials in observation time or research design, we needed more post-market real-world studies to obtain more information on infection occurrence. Analysis of reports of infections with inhaled or nasal corticosteroids using FAERS data complemented research in this area. Our results were consistent with previous studies and guidelines,[1] which indicated that ICS or INCs might increase the risk of infection.

As shown in Table 1, the proportion of women infected using ICS or INCs was exponentially higher than that of men. A study analyzed gender differences in AE reports submitted by over 100 countries worldwide collected in the VigiBase database from 1967 to 2018.[11] The results showed that 60.1% of AE reports came from women and 39.9% from men. However, there was no evidence that women had a higher proportion than men in the incidence rate of COPD, asthma, or allergic rhinitis. Therefore, the explanation for our research findings might be that female patients who used ICS or INCs were more likely to detect the occurrence of AE and actively report it, or indeed women were more at risk of infection. Table 1 shows that the average age of infected patients was 62.12 years old. Due to the unknown age of approximately 40% of reported infection AEs, it was unclear whether elderly individuals (over 65 years old) were more susceptible to infection. In addition, from the perspective of the reporting population, the proportion of infection reports from consumers was the highest, followed by those from physicians, which might be related to the attention and timely detection of AEs.

As shown in Table 2, the proportion of infections using ICS or INCs containing Fluticasone and Budesonide was similar. However, the proportion of pneumonia and oral fungal infections with Fluticasone (1.24%, 0.22%, respectively) was higher than that with Budesonide (0.86%, 0.10%, respectively). A systematic review study showed that compared to Budesonide users, Fluticasone users had a 13.5% increased risk of pneumonia and a 14.4% increased risk of severe pneumonia.[12] Another systematic review investigated the risk of pneumonia and severe pneumonia in Budesonide/Formoterol and Salmeterol/Fluticasone, and the results showed that the proportion of patients in the former was significantly lower than that in the latter.[13] An observational cohort study compared the incidence of thrush, an oral mucosal lesion caused by Candida albicans infection, in patients using Budesonide/Formoterol and Salmeterol/Fluticasone. The results showed that Salmeterol/Fluticasone-induced thrush was dose-dependent, and the incidence of thrush was higher in Salmeterol/Fluticasone dry powder inhalers (DPIs) than in Budesonide/Fomototerol DPI and Salmeterol/Fluticasone metered-dose inhalers (MDIs).[14] These research results were consistent with ours.

The mouth and respiratory tract were the main sites of infection caused by ICS and INCs. There have been many studies confirming that ICS causes pneumonia. We also analyzed the proportion of infections in upper respiratory tract areas such as the pharynx and nose. As shown in Table 3, the highest proportion of upper respiratory tract infections were reported to be caused by Mometasone (25.11%), while the lowest proportion was by Fluticasone (16.71%). However, this result was inconsistent with the results of a systematic evaluation study. The results showed that Fluticasone treatment significantly increased the risk of upper respiratory infections, especially at high doses, but Mometasone did not significantly increase.[15]

In our study, more than half of the infection reports did not identify the pathogenic bacteria. But based on the report name, we speculate that the possible pathogenic bacteria were bacteria. (Table 4). The reported incidence of fungal and viral infections in patients using Beclomethasone was the highest, while Fluticasone was similar to Budesonide and Triamcinolone was lower. Budesonide and Ciclesonide had a similar proportion of reported infections with Mycobacterium and were higher than other drugs. Until now, few studies have compared the risk of various pathogen infections caused by ICS or INCs. Our results were a supplement to existing research. A retrospective study evaluated whether pathogens discovered during acute exacerbation of chronic obstructive pulmonary disease (AECOPD) in 28 hospitals between 2008 and 2019 were associated with ICS used within the 6 months before AECOPD.[16] The results indicated that pathogenic specimens of AECOPD patients using ICS or ICS/LABA were more likely to isolate *M. Pneumonia*, especially those with frequent social activities and frequent travel to crowded areas, but were less likely to isolate Pseudomonas aeruginosa. A case-control study from 2012 to 2020 showed that the risk of *P. aeruginosa* infection in severe COPD patients was not related to the use of inhaled Fluticasone, but to the dosage of Fluticasone, and high doses of Fluticasone increased the risk of *P. aeruginosa* infection.[17] A retrospective study in South Korea showed that severe AECOPD patients who previously used ICS were more likely to detect virus positivity.[18] Meanwhile, studies have shown that compared to the respiratory respiratory syncytial virus (RSV) and coronavirus, rhinovirus and influenza

A virus were the most detected viruses in AECOPD patients who previously used ICS.[16] Studies showed that long-term use of ICS did not increase the risk of SARS-COV2 infection.[19,20] Multiple meta-analyses have shown that ICS could increase the risk of tuberculosis (TB) and non-tuberculosis mycobacterial (NTM) infections, and the higher the dosage of ICS, the more significant the risk. However, there was no significant difference in the risk of NTM infection among the Budesonide, Beclomethasone, and Fluticasone groups.[18,21]

As shown in Table 5, the monotherapy ICS appeared to have more infection-related adverse events than compound therapy, except for Glycopyrrolate/Indacaterol/Mometasone. There was a significant lack of information on the dosage form of Triamcinolone Acetonide in the infection report. Although we had tried to exclude Triamcinolone Acetonide injections, ointments, eye preparations, etc. based on the product name, route of administration, dosage, frequency of administration, remarks, etc., there were still 274 Triamcinolone Acetonide infection reports that could not be determined whether they were nasal preparations. The adverse reactions such as foot and central nervous system might be related to non-nasal preparations.

We presented the AE signal intensity of each ICS and INCs with bubble charts using the statistical indicators N, ROR, and $\chi 2$, as depicted in Figures 1–6. There was a significant difference in the AE signal intensity of inhalation and nasal formulations of Ciclesonide and Budesonide. To avoid bubble overlap, two bubble plots were used to describe them. Among the top 5 adverse events in signal intensity ranking, the use of ICS was associated with an increased risk of respiratory and fungal infections, while the use of INCs was associated with a higher risk of nasal and eye infections. Inhalation of Beclomethasone was more likely to be associated with oral infections, while inhalation of Budesonide with tuberculosis infections, and nasal use of Ciclesonide with mycobacterial infections. These were special signals that needed to be taken seriously.

The difficulties and deficiencies in this study were due to missing data in the obtained AE report. For example, there were many reports of severe missing dosing data, so dose stratification analysis could not be performed. However, multiple studies have shown that the risk of infection was related to the dosage of ICS or INCs.[17,18,22,23] In addition, as shown in Table 3, the reported incidence of eye infections caused by Triamcinolone Acetonide was significantly higher than other ICS or INCs. But these reports originated from Triamcinolone Acetonide of unclear dosage forms, which might be eye injections. At the same time, this study classifies AE reports according to SOC, one of which was “Eye infections, infection, and inflammation”, and did not distinguish between eye infections or non-infectious diseases. Due to the presence of multiple confounding factors, the higher risk of eye infection with Triamcinolone Acetonide might not be exact.

The use of ICS alone did not improve the FEV1 or mortality in COPD patients, so it was recommended to use it in combination with long-acting bronchodilators. But there might be overuse of drugs in clinical practice.[24–26] To reduce airway and fungal infections caused by inhaled corticosteroids, improper prescriptions should be avoided. It was necessary to avoid issuing ICS to COPD patients with recurrent pneumonia events, Blood eosinophils<100 cells/μL, and tuberculosis history.[1] Mastering the operation techniques of ICS or INCs devices and deep rinsing after ICS use could reduce the risk of infection. Therefore, physicians, nurses, or pharmacists should strengthen guidance on the use of ICS or INCs by patients, and promptly detect usage errors and adverse events of infection.

Conclusion

Based on the FAERS database, we evaluated the risk of infection caused by 6 ICS and INCs. Women who used ICS and INCs were more prone to infection events. Compared to Budesonide, Fluticasone seemed to have a higher risk of pneumonia and oral candidiasis. The use of Mometasone Furoate had a higher risk of upper respiratory tract infections. From the distribution of infected pathogens, Beclomethasone had more fungal and viral infections, while Ciclesonide and Budesonide had more mycobacterium infections. Airway and fungal infections were common high-risk adverse events for ICS, while INCs were nasal and ocular infections. However, oral infections should be noted when inhaling Beclomethasone. Therefore, we suggested that clinical healthcare professionals should provide training on drug-device operation for patients using ICS and INCs, as well as emphasize the importance of deep mouthwash after ICS use to reduce the occurrence of infections.

Ethics Statement

This study was approved by an institutional review board from the Third People's Hospital of Chengdu and conducted following the Declaration of Helsinki. This study did not involve intervention therapy or patient-sensitive information but publicly available data. Therefore, an application for exemption from ethical review was made.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the Sichuan Provincial Health Commission [grant numbers 18PJ539, 2018].

Disclosure

All authors have no conflicts of interest to declare for this work.

References

1. 2024 Gold Reports - Global initiative for chronic obstructive lung disease, GOLD; 2024. Available from: https://goldcopd.org/2024-gold-reports/. Accessed February 2, 2024.
2. 2023 GINA report, Global strategy for asthma management and prevention; 2024. Available from: https://ginasthma.org/2023-gina-main-report/. Accessed February 2, 2024.
3. Brożek JL, Bousquet J, Agache I, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. *J Allergy Clin Immunol*. 2017;140(4):950–958. doi:10.1016/j.jaci.2017.03.050
4. Yang IA, Ferry OR, Clarke MS, et al. Inhaled corticosteroids versus placebo for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2023;3(3):CD002991. doi:10.1002/14651858.CD002991
5. You Y, Ni Y, Shi G. Inhaled corticosteroids and mycobacterial infection in patients with chronic airway diseases: a systematic review and meta-analysis. *Respiration*. 2022;101(10):970–980. doi:10.1159/000525980
6. Ni J, Tang X, Chen L. Medication overdose data analysis: a review of medication error reports in the FDA adverse event reporting system (FAERS). *BMC Pharmacol Toxicol*. 2023;24(1):41. doi:10.1186/s40360-023-00681-y
7. Wei W, Chen L, Zhou H, et al. Safety profiles of methylphenidate, amphetamine, and atomoxetine: analysis of spontaneous reports submitted to the food and drug administration adverse event reporting system. *Front Pharmacol*. 2023;14:1208456. doi:10.3389/fphar.2023.1208456
8. Sakaeda T, Tamon A, Kadoyama K, et al. Data mining of the public version of the FDA adverse event reporting system. *Int J Med Sci*. 2013;10(7):796–803. doi:10.7150/ijms.6048
9. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). *Drug Saf*. 1999;20(2):109–117. doi:10.2165/00002018-199920020-00002
10. Evans SJ, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. *Pharmacoepidemiol Drug Saf*. 2001;10(6):483–486. doi:10.1002/pds.677
11. Watson S, Caster O, Rochon PA, et al. Reported adverse drug reactions in women and men: aggregated evidence from globally collected individual case reports during half a century. *EClinicalMedicine*. 2019;17:100188. doi:10.1016/j.eclinm.2019.10.001
12. Lodise TP, Li J, Gandhi HN, et al. Intraclass difference in pneumonia risk with fluticasone and budesonide in COPD: a systematic review of evidence from direct-comparison studies. *Int J Chron Obstruct Pulmon Dis*. 2020;15:2889–2900. doi:10.2147/COPD.S269637
13. Halpin DM, Gray J, Edwards SJ, et al. Budesonide/formoterol vs. salmeterol/fluticasone in COPD: a systematic review and adjusted indirect comparison of pneumonia in randomised controlled trials. *Int J Clin Pract*. 2011;65(7):764–774. doi:10.1111/j.1742-1241.2011.02685.x
14. Dekhuijzen PNR, Batsiou M, Bjermer L, et al. Incidence of oral thrush in patients with COPD prescribed inhaled corticosteroids: effect of drug, dose, and device. *Respir Med*. 2016;120:54–63. doi:10.1016/j.rmed.2016.09.015
15. Yang M, Chen H, Zhang Y, et al. Long-term use of inhaled corticosteroids and risk of upper respiratory tract infection in chronic obstructive pulmonary disease: a meta-analysis. *Inhal Toxicol*. 2017;29(5):219–226. doi:10.1080/08958378.2017.1346006
16. Sim YS, Lee JH, Lee EG, et al. COPD exacerbation-related pathogens and previous COPD treatment. *J Clin Med*. 2022;12(1):111. doi:10.3390/jcm12010111
17. Shafiek H, Verdú J, Iglesias A, et al. Inhaled corticosteroid dose is associated with Pseudomonas aeruginosa infection in severe COPD. *BMJ Open Respir Res*. 2021;8(1):e001067. doi:10.1136/bmjresp-2021-001067
18. Jang JG, Ahn JH, Jin HJ. Incidence and prognostic factors of respiratory viral infections in severe acute exacerbation of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2021;16:1265–1273. doi:10.2147/COPD.S306916
19. Chen CH, Chen CY, Lai CC, et al. The association between inhaled corticosteroid and the risks of SARS-COV-2 infection: a systematic review and meta-analysis. *J Infect Public Health*. 2023;16(5):823–830. doi:10.1016/j.jiph.2023.03.019
20. Chen RD, Yang CW, Chen XB, et al. Therapeutic efficacy of nasal corticosteroids in COVID-19-related olfactory dysfunction: a comprehensive systematic review and meta-analysis. *Otolaryngol Head Neck Surg*. 2024;170(4):999–1008. doi:10.1002/ohn.621

21. Castellana G, Castellana M, Castellana C, et al. Inhaled corticosteroids and risk of tuberculosis in patients with obstructive lung diseases: a systematic review and meta-analysis of non-randomized studies. *Int J Chron Obstruct Pulmon Dis*. 2019;14:2219–2227. doi:10.2147/COPD.S209273
22. George MD, Baker JF, Winthrop K, et al. Risk for serious infection with low-dose glucocorticoids in patients with rheumatoid arthritis: a cohort study. *Ann Intern Med*. 2020;173(11):870–878. doi:10.7326/M20-1594
23. Martinez-Garcia MA, Faner R, Oscullo G, et al. Inhaled steroids, circulating eosinophils, chronic airway infection, and pneumonia risk in chronic obstructive pulmonary disease: a network analysis. *Am J Respir Crit Care Med*. 2020;201(9):1078–1085. doi:10.1164/rccm.201908-1550OC
24. Cataldo D, Derom E, Liistro G, et al. Overuse of inhaled corticosteroids in COPD: five questions for withdrawal in daily practice. *Int J Chron Obstruct Pulmon Dis*. 2018;13:2089–2099. doi:10.2147/COPD.S164259
25. Turan O, Emre JC, Deniz S, et al. Adherence to current COPD guidelines in Turkey. *Expert Opin Pharmacother*. 2016;17(2):153–158. doi:10.1517/14656566.2016.1115482
26. White P, Thornton H, Pinnock H, et al. Overtreatment of COPD with inhaled corticosteroids – implications for safety and costs: cross-sectional observational study. *PLoS One*. 2013;8(10):e75221. doi:10.1371/journal.pone.0075221